RECEIVED
CENTRAL FAX CENTER

SEP 16 2005

BEFORE THE BOARD OF APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. 09/977,155

Applicant: Herz et al.

Filed: October 12, 2001

Docket No. UTSD:0862

Title: *LDL Receptor Signaling Assays*

Customer No. 23379

Confirmation No. 3854

Group Art Unit: 1641

Examiner: Cook, L.

CERTIFICATE OF TRANSMISSION
I hereby certify that this corr is being transmitted by facsimile to the Comm for Patent 571-273-8300 on September 16, 2005.

Signed _____
Richard Aron Osman

BRIEF ON APPEAL

The Honorable Board of Appeals and Interferences
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Honorable Board:

We appeal from the May 18, 2005 final rejection of claims 1-9 and 11-20.

REAL PARTY IN INTEREST

The real party in interest is The University of Texas System Board of Regents, the assignee of this application.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals or interferences.

STATUS OF CLAIMS

Claims 1-9 and 11-20 are rejected and subject to this appeal. Pending claim 10 is allowable and objected to as being dependent upon a rejected base claim.

09/19/2005 TL0111 00000047 09977155
01 FC:1402 500.00 OP

STATUS OF AMENDMENTS

All Amendments are believed to be properly before the Board.

SUMMARY CLAIMED SUBJECT MATTER

The invention provides methods and compositions for modeling and detecting LDL receptor transmembrane signaling by detecting proteolysis of an LDL receptor transmembrane domain. The method generally comprises the steps of: a) providing a sample comprising a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a C-terminal tail, and (ii) a protease which specifically cleaves the domain and thereby releases the tail from the membrane; b) incubating the sample under conditions wherein the protease cleaves the domain and thereby releases the tail from the membrane; and c) detecting a resultant released tail, which indicates proteolysis of the LDL receptor transmembrane domain. Frequently, the sample further comprises a candidate agent which modulates the resultant cleavage and/or release, wherein an agent-biased cleavage and/or release is detected. Specification, p.2, lines 2-11.

In one embodiment wherein the sample comprises a viable cell which comprises the membrane, the tail comprises an intracellular transcription factor domain, the cell further comprises a transcriptional reporter responsive to release of the transcription factor domain from the membrane, and the detecting step comprises detecting expression of the reporter as an indication of the released tail. In another embodiment the sample comprises a cellular membrane extract which comprises the membrane, and the detecting step comprises selectively detecting released, soluble tails, such as by solid-phase affinity adsorption assay. Specification, p.2, lines 12-19.

In other embodiments, the transmembrane domain is that of an LDL receptor selected from the group consisting of LRP, LRP1b, megalin, LDLR, VLDLR, ApoER2, MEGF7, LRP5, LRP6 and LR11, particularly LRP, LRP1b or megalin. The tail may comprise the native cytoplasmic domain of the LDL receptor or a truncation thereof, either of which may be fused to a transcription factor domain, an affinity tag, a label, etc. Alternatively, the tail may comprise an exclusively heterologous sequence. The recited protease is preferably native to the membrane, particularly gamma secretase. The subject compositions include systems and kits for the disclosed LDL receptor signaling assays. Specification, p.2, lines 20-27.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. WHETHER THE EXAMINER HAS PROPERLY REJECTED CLAIMS 1-9 and 11-14 UNDER 35USC102(b).

II. WHETHER THE EXAMINER HAS PROPERLY REJECTED CLAIMS 15-20 UNDER 35USC103(a).

ARGUMENT

I. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIMS 1-9 and 11-14 UNDER 35USC102(b).

Willnow et al. (1994, J Biol Chem 269, 15827-32) describe the production and functional analysis of truncated LRPs comprising subsets of the of the native N-terminal, extracellular domains (Fig. 1). One minireceptor was partially cleaved at a known region IV proteolytic processing site (Fig. 2A, lanes 2 and 4). LRP is known to be naturally proteolyzed at this extracellular N-terminal protcolytic processing site to generate two subunits: a 85 kd membrane spanning beta subunit, and a larger 515 kd N-terminal alpha-subunit which lacks a membrane-spanning region, but remains attached to the membrane through noncovalent association with the smaller C-terminal beta-subunit (Herz et al. (1990, EMBO J 9, 1769-1776).

The present inventors disclose that LRP and other members of the LDL receptor gene family undergo distinct endoprotcolytic processing events *that result in the release of their cytoplasmic tails into the cytoplasm.* Specification, p.1, liens 24-26. To release a cytoplasmic tail, the disclosed processing need to occur at intramembranous or cytoplasmic sites – not the N-terminal, extracellular region IV processing site known in the art, which liberates an extracellular domain, and not a cytoplasmic tail.

Accordingly, all our claimed methods are for detecting protcolysis of an LDL receptor transmembrane domain, and require a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a C-terminal tail, and (ii) a protease which specifically cleaves the domain and thereby releases the tail from the membrane. In contrast, Willnow describes an LRP which is cleaved at an N-terminal, extracellular site, and the protease does not and cannot release from the membrane any C-terminal tail.

The Examiner correctly observes that Willnow et al. describe using an anti-LRP antibody

directed against the cytoplasmic tail of LRP to identify unprocessed precursor (region IV) and the processed 85-kDa carboxyl-terminal fragment (Fig 2; para. bridging p.15828-15829) on immunoblots made from extracted and partially purified membrane proteins. Accordingly, in Willnow the carboxyl-terminal fragment is released from the membrane not by the protease, but rather by subsequent biochemical extraction. In Willnow, protease cleavage at the N-terminal, extracellular region IV processing site yields a membrane-bound fragment. The membrane-bound C-terminal cleavage produce is then biochemically extracted from the membrane. In contrast, our claims require that cleavage by the protease release the tail from the membrane, which does not and cannot occur in Willnow's work.

There appears to be no dispute that the disclosed invention is patentable over the cited art, but only whether a critical feature of the invention (cleavage at intramembrane or cytoplasmic sites) is recited in the claims (e.g. 6-16-05 Advisory Action, p.5, lines 1 - 15). The Action construes the claims to merely require "a protease that cleaves a domain and releases a tail from the membrane." 6-16-05 Advisory Action, p.5, lines 1–18. However, this quotation strategically omits a critical word from our claim, eliminating a required causality, and effectively changing the substance of the claimed invention.

Steps (b) and (c) of claim 1 read as follows:

> b) incubating the sample under conditions wherein the protease cleaves the domain and thereby releases the tail from the membrane; and
>
> c) detecting a resultant released tail, which indicates proteolysis of the LDL receptor transmembrane domain.

Note that "the protease cleaves the domain and *thereby* releases the tail from the membrane". The claim expressly and affirmatively *requires* that release of the tail result from the protease cleavage. If cleavage does not effect release of the tail, but rather the tail is released by some independent mechanism, such as biochemical extraction, our claim is not infringed. This requirement is furthered in step (c) wherein the "*resultant* released tail" is detected – not any released tail, but only a tail released as a result of the protease cleavage recited in step (b), and not a tail released as a result of some independent mechanism, such as biochemical extraction.

Even if the causality requirement of our claim was relegated to a terminal "whereby

clause", it still could not be properly disregarded ("when the "whereby" clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention. Hoffer v. Microsoft Corp., Case No. 04-1103 (Fed. Cir. Apr. 22, 2005)). In our case however, the causality limitation is an inextractable requirement of expressly and affirmatively recited method steps (b) and (c).

In an effort to resolve this difference in claim construction, we offered to provide or approve any equivalent claim language preferred by the Examiner that similarly requires that the release of the tail result from the recited protease cleavage (Response filed Jun 25, 2005). We remain pleased to do so.

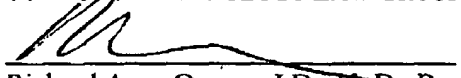
II. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIMS 15-20 UNDER 35USC103(a).

Willnow has been described above. Herz (2001, Neuron 29, 571-81) describes LDL receptor family proteins, and reviews the diverse physiological roles that these receptors have been found to play. However, nowhere does Herz disclose or suggest producing and detecting a protease liberated C-terminal tail of any LDR receptor as required by our claims.

Appellants respectfully request reversal of the pending Final Action by the Board of Appeals.

The Appeal Brief Fee is provided in the attached PTO-2038. We petition for and authorize charging our Deposit Account No.19-0750 all necessary extensions of time. The Commissioner is authorized to charge any fees or credit any overcharges relating to this communication to our Dep. Acct. No.19-0750 (order UTSD:0862).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP



Richard Aron Osman, J.D., Ph.D., Reg.No. 36,627
Tel(949) 218-1757; Fax(949) 218-1767

"To Help Our Customers Get Patents"
Mission Statement, USPTO External Customer Services Guide

EVIDENCE APPENDIX

None of record.

RELATED PROCEEDINGS APPENDIX

No related proceedings are known to exist.

CLAIMS APPENDIX

1. A method for detecting proteolysis of an LDL (Low Density Lipoprotein) receptor transmembrane domain, comprising the steps of:

a) providing a sample comprising a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a C-terminal tail, and (ii) a protease which specifically cleaves the domain and thereby releases the tail from the membrane;

b) incubating the sample under conditions wherein the protease cleaves the domain and thereby releases the tail from the membrane; and

c) detecting a resultant released tail, which indicates proteolysis of the LDL receptor transmembrane domain.

2. A method according to claim 1, wherein the sample comprises a viable cell which comprises the membrane.

3. A method according to claim 1, wherein the sample comprises a viable cell which comprises the membrane, the tail comprises an intracellular transcription factor domain, the cell further comprises a transcriptional reporter responsive to release of the transcription factor domain from the membrane, and the detecting step comprises detecting expression of the reporter as an indication of the released tail.

4. A method according to claim 1, wherein the sample comprises a cellular membrane extract which comprises the membrane.

5. A method according to claim 1, wherein the sample comprises a cellular membrane extract which comprises the membrane, and the detecting step comprises selectively detecting released, soluble tails.

6. A method according to claim 1, wherein the sample comprises a cellular membrane extract which comprises the membrane, and the detecting step comprises selectively detecting released, soluble tails by solid-phase affinity adsorption assay.

7. A method according to claim 1, wherein the tail comprises an affinity tag.

8. A method according to claim 1, wherein the tail comprises at least a portion of the cytoplasmic domain of the LDL receptor.

9. A method according to claim 1, wherein the protease is native to the membrane.

10. (Objected to only) A method according to claim 1, wherein the protease is gamma secretase.

11. A method according to claim 1, wherein the LDL receptor is selected from the group consisting of LRP (LDL Receptor-related Protein), LRP1b (LDL Receptor-related Protein 1b), megalin, LDLR (Low Density Lipoprotein Receptor), VLDLR (Very Low Density Lipoprotein Receptor), ApoER2 (Apolipoprotein E Receptor 2), MEGF7 (Multiple Epidermal Growth Factor-like domain protein 7), LRP5 (Low density lipoprotein Receptor-related Protein 5), LRP6 (Low density lipoprotein Receptor-related Protein 5) and LR11 (Low density lipoprotein Receptor 11).

12. A method according to claim 1, wherein the LDL receptor is LRP and the protease is native to the membrane.

13. A method according to claim 3, wherein the LDL receptor is LRP and the protease is native to the membrane.

14. A method according to claim 5, wherein the LDL receptor is LRP and the protease is native to the membrane.

15. A method according to claim 1, wherein the LDL receptor is LRP1b and the protease is native to the membrane.

16. A method according to claim 3, wherein the LDL receptor is LRP1b and the protease is native to the membrane.

17. A method according to claim 5, wherein the LDL receptor is LRP1b and the protease is native to the membrane.

18. A method according to claim 1, wherein the LDL receptor is megalin and the protease is native to the membrane.

19. A method according to claim 3, wherein the LDL receptor is megalin and the protease is native to the membrane.

20. A method according to claim 5, wherein the LDL receptor is megalin and the protease is native to the membrane.